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| EXAMINER |
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HAMA, JOANNE

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| ART UNIT | PAPER NUMBER |
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1632

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|--|------------|---------------|
| 3 MONTHS | 04/23/2007 | PAPER |

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| | | | |
|------------------------------|---------------------------------------|---|--|
| Office Action Summary | Application No. 10/049,849 | Applicant(s) VELANDER, WILLIAM HUGOLD | |
| | Examiner Joanne Hama, Ph.D. | Art Unit 1632 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 22 January 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,5-8,11-13,16,17,20,22,24,25,27,40,42,44,46,53 and 56-61 is/are pending in the application.
- 4a) Of the above claim(s) 1,5-8,11-13,16,17,20,22,24,25,27,53 and 59 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 40,42,44,46,56-58,60 and 61 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 22, 2007 has been entered.

Claims 2-4, 9, 10, 14, 15, 18, 19, 21, 23, 26, 28-39, 41, 43, 45, 47-52, 54, 55 are cancelled. Claims 1, 5-8, 11-13, 16, 17, 20, 22, 24, 25, 27, 53, 59 are withdrawn.

Claims 40, 44 are amended. Claims 60, 61 are new.

Claims 40, 42, 44, 46, 56-58, 60, 61 are under consideration.

Withdrawn Rejections

35 U.S.C. § 112, 2nd parag.

Applicant's arguments, see pages 9-10 of Applicant's response, filed January 22, 2007, with respect to claims 40, 42, 46, 50, 56-58 have been fully considered and are persuasive. Applicant indicates that claims 40 and 44 have been amended to include the phrase, "amino acid sequence." The rejection of claims 40, 42, 46, 56-58 has been withdrawn. It is noted that the rejection of claim 50 is withdrawn as claim 50 is cancelled.

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35 U.S.C. § 102

Applicant's arguments, see page 10 of Applicant's response, filed January 22, 2007, with respect to the rejection of claims 40, 42, 44, 46, 56, 58 as being anticipated by Wu et al., 1997, have been fully considered and are persuasive. Applicant indicates that claim 40 recites, "milk derived from a transgenic mammal." The rejection of claims 40, 42, 44, 46, 56, 58 has been withdrawn.

Applicant's arguments, see page 10-11 of Applicant's response, filed January 22, 2007, with respect to the rejection of claims 40, 42, 44, 46, 56, 58 as being anticipated by Wu and Suttie, 1999, as evidenced by Wu et al., 1997, have been fully considered and are persuasive. Applicant indicates that claim 40 recites, "milk derived from a transgenic mammal." The rejection of claims 40, 42, 44, 46, 56, 58 has been withdrawn.

Applicant's arguments, see page 10-11 of Applicant's response, filed January 22, 2007, with respect to the rejection of claims 40, 42, 44, as being anticipated by Wu and Suttie, 1999, have been fully considered and are persuasive. Applicant indicates that claim 40 recites, "milk derived from a transgenic mammal." The rejection of claims 40, 42, 44 has been withdrawn.

Applicant's arguments, see page 10-11 of Applicant's response, filed January 22, 2007, with respect to the rejection of claims 40, 44, 57 as being anticipated by Seegers et al., 1950, have been fully considered and are persuasive. Applicant indicates that claim 40 recites, "milk derived from a transgenic mammal." The rejection of claims 40, 44, 57 has been withdrawn.

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Applicant's arguments, see page 10-11 of Applicant's response, filed January 22, 2007, with respect to the rejection of claims 40, 42, 44, 57 as being anticipated by Vogel et al., 1976, have been fully considered and are persuasive. Applicant indicates that claim 40 recites, "milk derived from a transgenic mammal." The rejection of claims 40, 42, 44, 57 has been withdrawn.

Applicant's arguments, see page 10-11 of Applicant's response, filed January 22, 2007, with respect to the rejection of claims 40, 42, 44, 57 as being anticipated by Landaburu and Seegers, 1958, have been fully considered and are persuasive. Applicant indicates that claim 40 recites, "milk derived from a transgenic mammal." The rejection of claims 40, 42, 44, 57 has been withdrawn.

35 U.S.C. § 103

Applicant's arguments, see pages 12-14 of Applicant's response, filed January 22, with respect to the rejection of claims 40, 42, 44, 46, 56-58 as being unpatentable over Wu and Suttie, 1999 in view of Seegers et al., 1950, have been fully considered and are persuasive. Claim 40 has been amended to include the phrase, "milk derived from a transgenic mammal." Applicant has provided a response rebutting the references used in the 103; however, the Examiner found the amendment to claim 40 to be persuasive as neither Wu and Suttie or Seegers to teach that prothrombin was secreted in milk. The rejection of claims 40, 42, 44, 46, 56-58 has been withdrawn.

New/Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40, 42, 44, 46, 56-58 remain rejected and new claims 60, 61 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record December 29, 2005 and September 19, 2006.

Applicant's arguments, see pages 7-9 of Applicant's response, filed January 22, 2007, have been fully considered and are persuasive in part.

With regard to the Examiner indicating that the specification does not teach a completely carboxylated Gla domain of prothrombin (Office Action, September, 19, 2006, page 5), Applicant indicates that page 41 of the specification teaches that fully-carboxylated recombinant prothrombin was made from the transgenic mammal (Applicant's response, page 8). The rejection as it applies to this issue is withdrawn.

With regard to the Examiner indicating that the specification does not give guidance for an artisan to arrive at recombinant prothombin-thrombin that have activity yet have different structures, Applicant indicates that on page 24, lines 14-22 of the specification teaches that there is support for specific amino acid changes that may be

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made in a prothrombin sequence and still maintain activity (Applicant's response, page 8). In response, this is not persuasive because while the citation from the specification teaches changes to glycosylation sites and lists a number of possible single mutations (Asn-79, Asn-101, and Asn-378) and an Asn-Leu Ser site at Asn-165, the changes listed do not give guidance for an artisan to change 30% of the sequence such that the protein is 70% identical to prothrombin and has the same biological activity of prothrombin. In addition to this issue, the art teaches that there are a number of sequences called "prothrombin." In addition to the 259 amino acid sequence taught by Degen and Davie, *Biochemistry*, 1987, 26: 6165-6177, Figure 4, an NCBI database search has also pulled up a prothrombin sequence (AAR08142) [retrieved on 2007-04-02] Retrieved from the Internet:< URL: <http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=protein&val=38018090>>, pages 1-2, that is 295 amino acids long and an amino acid sequence (AAC63054) [retrieved on 2007-04-02]. Retrieved from the Internet:< URL: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=protein&cmd=&term=aac63054>, pages 1-2, that is 622 amino acids long. (Copies of these sequences have been provided.) A BLAST using AAR08142 pulled up *Xenopus* Lpa-prov protein that is 71% identical to AAR08142. A search of the sequence does not indicate whether or not Lpa-prov is prothrombin or not and thus, it is not clear what characteristics comprise a prothrombin such that an artisan can readily obtain any prothrombin. As such, because it is not clear what sequence is "prothrombin", it is unclear what 30% of the sequence can be

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changed such that an artisan can readily identify a sequence as prothrombin. The rejection as it applies to this issue remains.

Applicant refers to the teachings of Degen that prothrombin modifications are not limited to glycosylation sites and indicates that Degen teaches, "(b)oth of these regions appear to be flexible in accommodating insertions or deletions and also have a high degree of amino acid substitutions between species (Applicant's response, page 9)." In response, it is not entirely clear what regions Degen is referring to such there is flexibility in accommodating insertions and deletions. It is noted that Applicant refers to the teachings of Degen; however, because there appears to be no copy on file of the reference, the Examiner cannot determine what guidance Degen gives about the protein sequence of prothrombin such that the claimed protein can be obtained.

Thus, the claims remain rejected.

Claims 40, 42, 44, 46, 56-58 remain rejected and new claims 60, 61 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record, December 29, 2005. It is noted that the Written Description was incorporated with the Enablement rejection, Office Action, September 19, 2006. It is noted that the Written Description rejection is a separate rejection and thus, the issues at hand of December 29, 2005 are reiterated here.

As indicated in the Office Action, December 29, 2005, the Written Description rejection was raised because while the specification indicates that particular mutations can occur in the prothrombin protein sequence, the specification does not provide guidance for an artisan to arrive at the full breadth of sequences that have the activity of prothrombin and have 30% of the human prothrombin sequence mutated. In addition to this issue, it is not clear what the sequence of prothrombin is; the art teaches a number of sequences that are called "prothrombin," yet the prothrombins have different amino acid lengths. Because there are a number of different prothrombin sequences, it is also unclear which sequence can be mutated 30%, have the activity of prothrombin, and be encompassed by the claims. Note, for example, that when BLASTing prothrombin, AAR08142, a *Xenopus* Lpa-prov protein that is 71% identical to prothrombin was identified. While Lpa-prov protein is at least 70% identical to AAR08142, it is not entirely clear if Lpa-prov has activity of a prothrombin such that it is encompassed by the claims. As such, because it is unclear what structures/functions of prothrombin are encompassed by the claims, "prothrombin" and "thrombin" lack Written Description. The rejection as it applies to this issue remains.

Applicant indicates that new claims 60, 61 recite that the first amino acid sequence has "at least 95%" and "at least 100%" identity to a human prothrombin amino acid sequence. Applicant indicates these percents of identity are well accepted to inherently retain the activity of the parent polypeptide. Applicant refers to Example 14 of the Revised Interim Written Description Guidelines Training Materials (Applicant's response, page 9). In response, this is not persuasive because according to the

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Example 14 of the Guidelines, the claim also indicates that the claimed protein has a particular function, i.e., that it catalyzes a reaction from A to B. Applicant's citation of the specification, page 9, lines 3-5, do not indicate any particular activity that is monitored. As such, claims 60 and 61 do not overcome the rejection at hand.

Thus, the claims remain rejected.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 61 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 61 is confusing because it is unclear how the lower limit of identity for a protein sequence is 100%. The wording implies that there is an upper limit of identity that is more than 100%. It is unclear how a sequence can have more than 100% identity.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 40, 60, 61 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Butler, 1997, Production and Secretion of Recombinant Human Fibrinogen by the Transgenic Murine Mammary Gland, Master of Science Thesis, Blacksburg, VA in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734 and in view of van Cott and Velandar, 1998, Expert Opinion on Investigational Drugs, 7: 1683-1690.

Butler teaches that a transgene construct comprising the coding region of the human fibrinogen chain was inserted between the 4.2 kbp ovine beta-lactoglobulin promoter and its associated 2.5kbp 3' untranslated region (UTR). The construct was injected into pronuclear phase murine or ovine zygotes. Transgenic founder animals were identified and recombinant fibrinogen was identified in the milk of the transgenic animals. In one case, one ewe produced about 5g/liter of recombinant protein (Butler, page 8, under "Expression of rhfib in transgenic mice and sheep"). While Butler teaches making recombinant fibrinogen in milk, Butler teaches that making other plasma-derived proteins would be possible in using transgenic mammals. Butler teaches that the advantages of making other recombinant plasma-derived proteins in milk include obtaining plasma-derived proteins which would be pathogen-free and obtaining proteins which are cost effectively abundant (Butler, page 2, under "Potential uses for recombinant human fibrinogen"). Particularly for the fibrin sealant (FS)-technologies, large amounts of pathogen-free thrombin are desirable (Butler, pages 2-3, under "Potential uses for recombinant human fibrinogen").

While Butler teaches making recombinant fibrinogen in the milk of transgenic mammals, Butler does not teach making recombinant human prothrombin.

Jorgensen et al. teach that human prothrombin cDNA was expressed in mammalian cells and yielded biologically active, fully gamma-carboxylated prothrombin (Jorgensen et al., abstract). Jorgensen et al. teach that expression vector comprising the coding sequence of human prothrombin was used to express in Chinese Hamster Ovary (CHO) cells and that up to 0.55 ug/ml of prothrombin protein was detected in the culture media (Jorgensen et al., page 6731, 1st col., under "Expression of Recombinant Prothrombin in Chinese Hamster Ovary Cells").

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the nucleic acid sequence encoding human fibrinogen with a nucleic acid sequence encoding human prothrombin.

One having ordinary skill in the art would have been motivated to substitute these sequences one for the other because Butler teaches that there is a need in the art for human recombinant plasma proteins (of which, prothrombin is one) that is pathogen-free. Also, Butler teaches that expressing proteins in milk is cost-effectively abundant. In addition to this, one would have been motivated to use the system taught by Butler because there is a higher yield of prothrombin in milk (5 g/liter) than in a mammalian cell expression system (0.55 ug/ml).

There would have been a reasonable expectation of success given the results of Butler for teaching that human fibrinogen was expressed in large quantities in milk.

With regard to the particular embodiment that prothrombin has a completely gamma-carboxylated Gla domain (claim 40), an artisan would have expected at least a fraction of the prothrombin Gla domain to be gamma-carboxylated. According to van Cott and Velander, while transgenic mice were poor at gamma-carboxylating recombinant proteins, transgenic pigs were able to gamma-carboxylate recombinant proteins excreted in milk up to 0.1 g/l/h (van Cott and Velander, page 1686, 2nd col., 3rd parag.).

Claims 40, 42, 44, 46, 56, 58 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Butler, 1997, Production and Secretion of Recombinant Human Fibrinogen by the Transgenic Murine Mammary Gland, Master of Science Thesis, Blacksburg, VA in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734 and in view of Le Bonniec et al., 1991, The Journal of Biochemistry, 266: 13796-13803, previously cited.

As indicated above, given the teaching of Butler, in view of Jorgensen et al., an artisan would have arrived at human prothrombin secreted in milk. While Butler and Jorgensen et al. provide this guidance, they do not teach that prothrombin is post-translationally modified by proteolytic processing.

Le Bonniec et al. teach that prothombin is activated by bovine factor Xa, in the presence of bovine factor Va, phospholipids, and calcium (Le Bonnic et al., page 13799, 1st col., 2nd parag.). It is noted that activation of prothrombin yields thrombin, the active form of the protein (e.g. see Le Bonniec, page 13796, 1st col., 1st parag.) and an artisan

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would want to make thrombin because Butler teaches that thrombin induces polymerization of fibrinogen, a protein involved in the blood coagulation cascade (Butler, page 2, under "Fibrinogen structure and function" and page 4, 2nd parag.).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to include a step of adding bovine factor Xa, factor Va, phospholipids, and calcium.

One having ordinary skill in the art would have been motivated to include bovine factor Xa, factor Va, phospholipids, and calcium, in order to obtain thrombin.

There would have been reasonable expectation of success given the results of Le Bonnic et al. for teaching that adding factor Xa, factor Va, phospholipids, and calcium activates prothrombin.

Claims 40 and 57 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Butler, 1997, Production and Secretion of Recombinant Human Fibrinogen by the Transgenic Murine Mammary Gland, Master of Science Thesis, Blacksburg, VA in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-2734 and in view of Seegers et al., 1950, Blood, 5: 421-433, previously cited.

As indicated above, given the teaching of Butler, in view of Jorgensen et al., an artisan would have arrived at human prothrombin secreted in milk. While Butler and Jorgensen et al. provide this guidance, they do not teach that prothrombin is post-translationally modified by proteolytic processing.

Seegers et al. teach that activation of purified prothrombin is accomplished by dissolving the purified prothrombin in a 25% solution of sodium citrate and allowing the mixture to stand at room temperature. After about 5 hours, measurable amounts of thrombin appear (Seegers et al., page 421, 3rd parag., pages 424-425 under "Activation of Prothrombin with Sodium Citrate," and Fig. 2). It is noted that activation of prothrombin yields thrombin, the active form of the protein, and that an artisan would want to make thrombin because Butler teaches that thrombin induces polymerization of fibrinogen, a protein involved in the blood coagulation cascade (Butler, page 2, under "Fibrinogen structure and function" and page 4, 2nd parag.).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to include a step of adding sodium citrate to prothrombin.

One having ordinary skill in the art would have been motivated to include sodium citrate, in order to obtain thrombin.

There would have been reasonable expectation of success given the results of Seegers et al. for teaching that addition of sodium citrate to prothrombin yields thrombin.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service

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center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JH

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to be 'AMW', is written over a long, thin, curved line that extends from the signature area towards the right margin of the page.